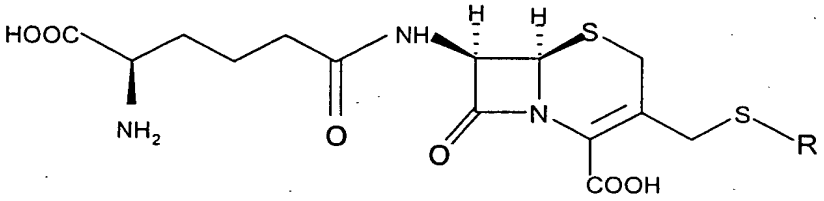
Claims

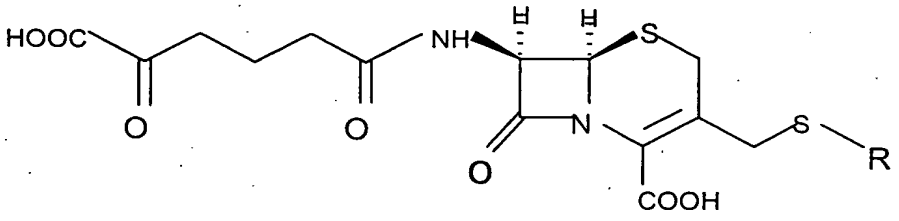
1. A process for preparing cephalosporanic acid derivatives comprising the steps of :-

enzymatically converting a 3-thiolated cephalosporin C compound of formula III:-



(III)

into a 3-thiolated-α-ketoadipyl-7-aminocephalosporanic acid derivative of formula IV:



(IV)

wherein R is a heterocyclic group comprising at least a nitrogen atom.

2. A process as claimed in claim 1 wherein the compound of formula III is enzymatically converted into a compound of formula IV by an immobilised enzyme system.

3. A process as claimed in claim 2 wherein the enzyme system comprises co-immobilised D-Amino acid oxidase and catalase.

4. A process as claimed in claim 3 wherein the enzymatic conversion is carried out in the presence of molecular oxygen, at a pressure of 1 to 5 bar absolute, a pH of from 6.5 to 8.0 and at a temperature of from 15 to 30°C for a period of from 30 mins to 180 mins.

5. A process as claimed in claim 1 comprising the step of separating the enzyme system from the reaction mixture, preferably by filtration.

6. A process as claimed in claim 1 including the step of purifying the compound of formula IV.

7. A process as claimed in claim 6 wherein the compound is purified using an adsorption column.

8. A process as claimed in claim 1 wherein the enzymes are co-immobilised using a suitable cross-linker agent in a suitable solid support.

9. A process as claimed in claim 8 wherein the enzymes are in the form of crystals of a size suitable for use as a biocatalyst.

10. A process as claimed in claim 1 wherein the enzymatic processes are carried out while maintaining the enzyme in dispersion in an aqueous substrate solution.

11. A process as claimed in claim 1 wherein the or each enzymatic process is carried out in a column.

12. A process as claimed in claim 1 including the step of recovering the enzyme for reuse.

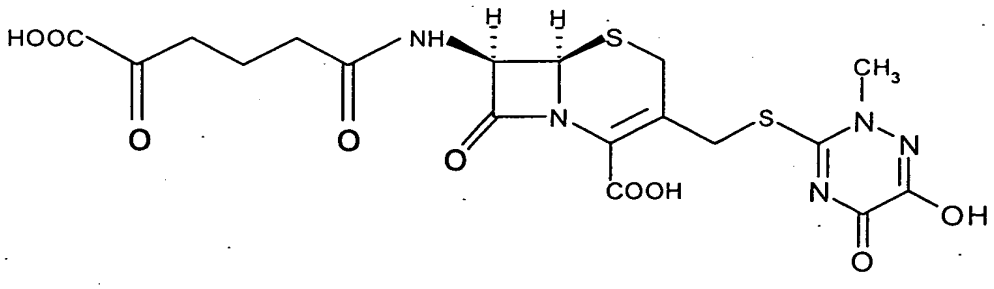
13. A process as claimed in claim 1 wherein the compound of formula IV is used without purification in a continuous process for obtaining any useful derivative.

14. A process as claimed in claim 1 wherein R is a heterocyclic group comprising at least one nitrogen atom and optionally a sulphur or oxygen atom.

15. A process as claimed in claim 14 wherein R is a heterocyclic group selected from any one or more of the group comprising thienyl, diazolyl, tetrazolyl, thiazolyl, triazinyl, oxazolyl, oxadiazolyl, pyridyl, pirimidinyl, benzo thiazolyl, benzimidazolyl, benzoxazolyl, or any derivative thereof, preferably 5-methyl-1,3,4-thiadiazol-2-yl, 1-methyl-1H-tetrazol-5-yl or 1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl.

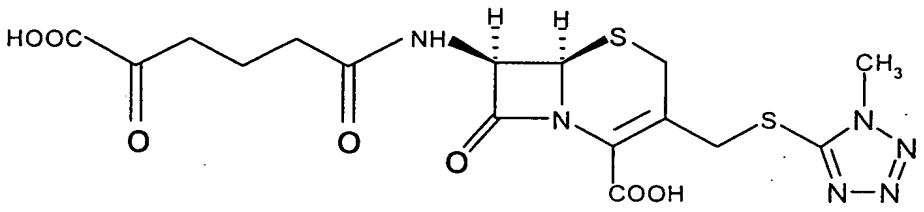
16. A 3-thiolated-α-ketoadipyl-7-aminocephalosporanic acid derivative of formula IV whenever prepared by a process as claimed in claim 1.

17. A compound of the Formula:-



wherein in formula IV, R is 1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl.

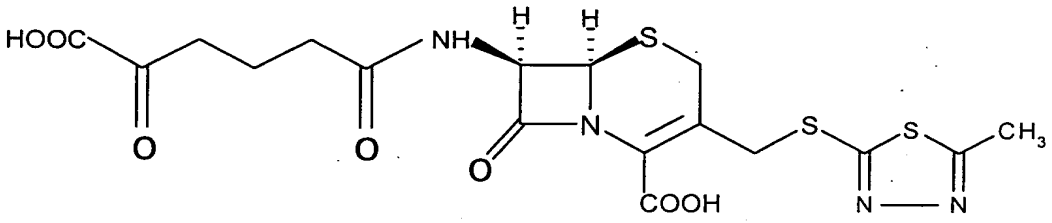
18. A compound of the Formula:-



wherein in formula IV, R is 1-methyl-1H-tetrazol-5-yl.

19. Use of a compound of formula IV as defined in claim 1 as an intermediate in a process for preparing cephalosporin C antibiotics.

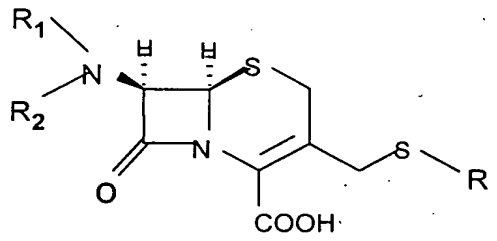
20. Use of an intermediate compound of the formula:-



in a process for preparing cephalosporin C antibiotics wherein in formula IV R is 5-methyl-1,3,4-thiadiazol-2-yl.

21. A process for preparing cephalosporanic acid derivatives as claimed in claim 1 comprising the step of:

enzymatically converting a compound of formula IV to form a compound of formula I



(I)

wherein R is a heterocyclic group comprising at least one nitrogen atom and R_1 and R_2 are both hydrogen atoms or one of them is a hydrogen atom and the other is an acyl donor.

22. A process as claimed in claim 21 wherein a compound of formula IV is enzymatically converted to form a compound of formula I using Glutaryl-7-ACA acylase.

23. A process as claimed in claim 21 wherein the enzymation takes place at a temperature of approximately 20°C and at a pH of between 6.5 and 8.0.

24. A process as claimed in claim 21 wherein the enzyme is immobilised using a suitable cross-linker agent in a suitable solid support.

25. A process as claimed in claim 24 wherein the enzyme is in the form of crystals of a size suitable for use as a biocatalyst.

26. A process as claimed in claim 21 wherein enzymation is carried out while maintaining the enzyme in dispersion in an aqueous substrate solution.

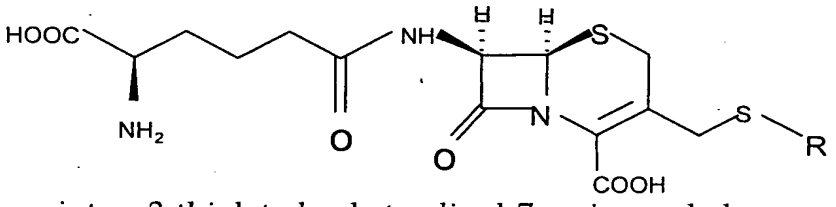
27. A process as claimed in claim 21 wherein the enzymatic process is carried out in a column.

28. A process as claimed in claim 21 including the step of recovering the enzyme for reuse.

29. Use of a compound of formula I as defined in claim 21 as an intermediate in a process for preparing cephalosporin C derivatives.

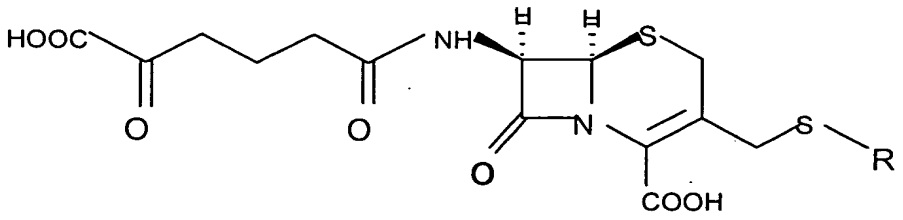
30. A process for preparing 3-thiolated cephalosporanic acid derivatives comprising the steps of;-

enzymatically converting a compound of formula III



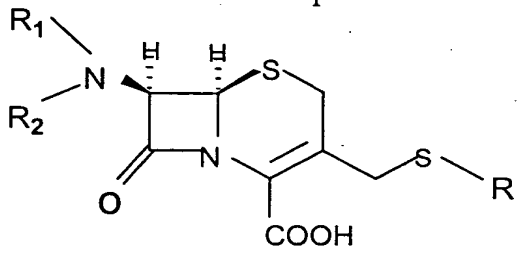
(III)

into a 3-thiolated-α-ketoadipyl-7-aminocephalosporanic acid derivative of formula IV:



(IV)

and enzymatically converting a compound of formula IV to form a 3-thiolated 7-ACA compound of formula I



(I)

wherein R is a heterocyclic group comprising at least one nitrogen atom and R_1 and R_2 are both hydrogen atoms or one of them is a hydrogen atom and the other is an acyl donor.

31. A process as claimed in claim 30 wherein the compound of formula III is enzymatically converted into a compound of formula I in one step by an immobilised enzyme system.

32. A process as claimed in claim 31 wherein the enzyme system comprises a combination of co-immobilised D-amino acid oxidase/catalase in the presence of immobilised Glutaryl-7-ACA acylase.

33. A process as claimed in claim 30 wherein the enzymation takes place at a temperature of approximately 20°C and at a pH of between 6.5 and 8.0.

34. A process as claimed in claim 30 wherein the enzymes are co-immobilised using a suitable cross-linker agent in a suitable solid support.

35. A process as claimed in claim 34 wherein the enzymes are in the form of crystals of a size suitable for use as a biocatalyst.

36. A process as claimed in claim 30 wherein the enzymatic processes are carried out while maintaining the enzyme in dispersion in an aqueous substrate solution.

37. A process as claimed in claim 30 wherein the or each enzymatic process is carried out in a column.

38. A process as claimed in claim 30 including the step of recovering the enzyme for reuse.

39. A process as claimed in claim 30 wherein the compound of formula III is used without purification in a continuous process for obtaining any useful derivative.

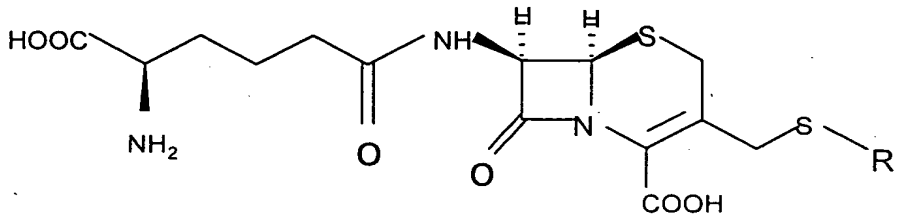
40. A process for preparing cephalosporanic acid derivatives comprising the steps of:-

reacting cephalosporin C with a thiol compound of the general formula II

R-SH II

wherein R is a heterocyclic group comprising at least one nitrogen atom,

to form a 3-thiolated cephalosporin Compound of formula III



(III)

wherein R is as defined above,

and, after formation of the compound of formula III removing excess thiol of formula II.

41. A process as claimed in claim 40 wherein the excess thiol is removed by adsorption on an anion exchange resin.

42. A process as claimed in claim 41 wherein the anion exchange resin is a microporous resin having a cross-linked acrylic copolymer structure.

43. A process as claimed in claim 42 wherein the anion exchange resin comprises an 8% cross-linking containing functional thialkyl benzyl ammonium group.

44. A process as claimed in claim 41 wherein the resin is in the chloride, hydroxy, phosphate or acetate cycle.

45. A process as claimed in claim 40 wherein the excess thiol is removed by crystallisation.

46. A process as claimed in claim 45 wherein crystallisation is carried out at an acidic pH.

47. A process as claimed in claim 40 wherein the excess thiol is removed by crystallisation followed by adsorption on an anion exchange resin.

48. A process as claimed in claim 40 wherein the cephalosporin C is in an aqueous medium.

49. A process as claimed in claim 40 wherein the cephalosporin C is in the form of a concentrated cephalosporin C solution.

50. A process as claimed in claim 40 wherein the reaction is carried out at a pH of between 5.5 and 8.0, at a temperature of from 60°C to 80°C, for a period of from 1 to 8 hours.

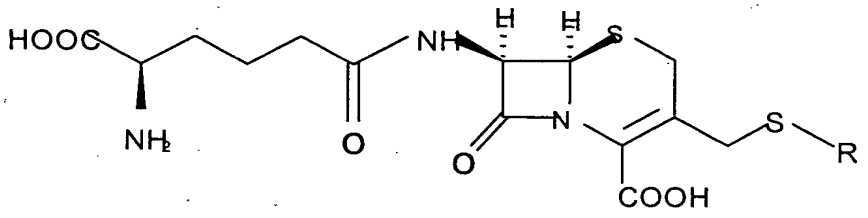
51. A process as claimed in claim 40 wherein the reaction is carried out at a pH of approximately 6.0 and at a temperature of approximately 65°C.

52. A process as claimed in claim 40 wherein the thiol compound is present in an amount of between 1 and 5 mol/mol of cephalosporin C.

53. A process as claimed in claim 40 wherein R is a heterocyclic group comprising at least one nitrogen atom and optionally a sulphur or oxygen atom.

54. A process as claimed in claim 40 wherein R is a heterocyclic group selected from any one or more of thienyl, diazolyl, thiazolyl, tetrazolyl, thiadiazolyl, triazinyl, oxazolyl, oxadiazolyl, pyridyl, pirimidinyl, benzothiazolyl, benzimidazolyl, benzoxazolyl, or any derivative thereof, preferably 5-methyl-1,3,4-thiadiazol-2-yl, 1-methyl-tetrazol-5-yl or 1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl.

55. A compound of formula III

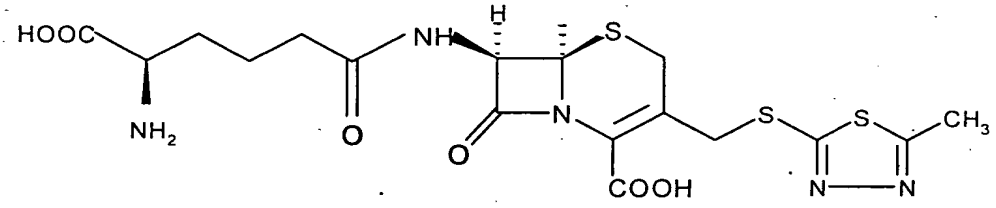


(III)

wherein R is a heterocyclic group comprising at least one nitrogen atom,

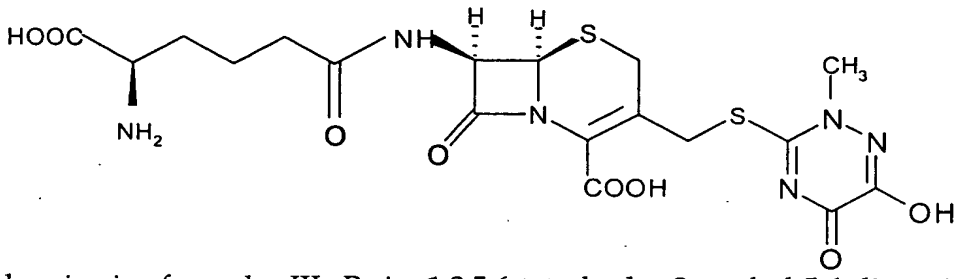
obtained by a process as claimed in any of claims 40 to 54.

56. A compound of the Formula:-



wherein in formula III R is 5-methyl-1,3,4-thiadiazol-2-yl.

57. A compound of the Formula:-

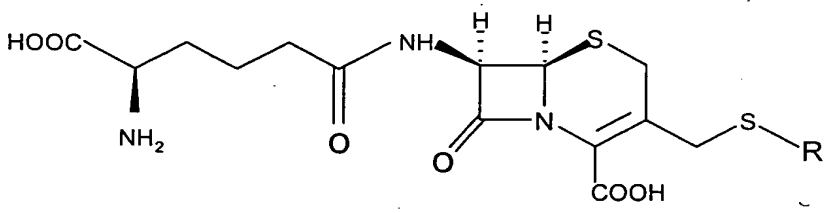


wherein in formula III R is 1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl.

58. Use of a compound of formula III as defined in claim 55 as an intermediate in a process for preparing cephalosporin C derivatives.

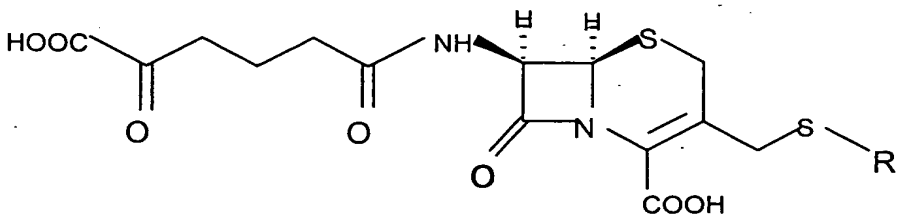
59. A process for preparing cephalosporanic acid derivatives comprising the steps of :-

enzymatically converting a 3-thiolated cephalosporin C compound of formula III obtained by a process as claimed in any of claims 40 to 54:-



(III)

into a 3-thiolated-α-ketoadipyl-7-aminocephalosporanic acid derivative of formula IV:

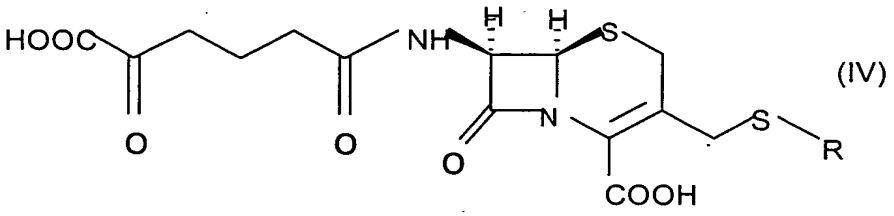


(IV)

wherein R is a heterocyclic group comprising at least a nitrogen atom.

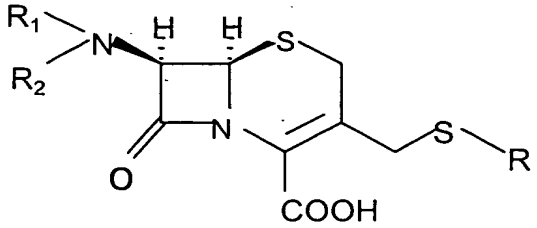
60. A process as claimed in claim 59 comprising the step of:

enzymatically converting a 3-thiolated α-ketoadipyl 7-ACA compound of formula IV



(IV)

to form a 3-thiolated 7-ACA compound of formula I

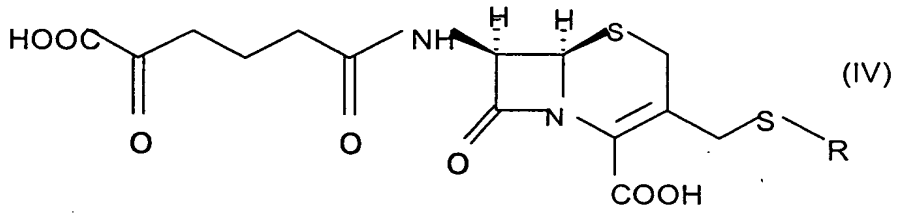


(I)

wherein R is a heterocyclic group comprising at least one nitrogen atom and R_1 and R_2 are both hydrogen atoms or one of them is a hydrogen atom and the other is an acyl donor.

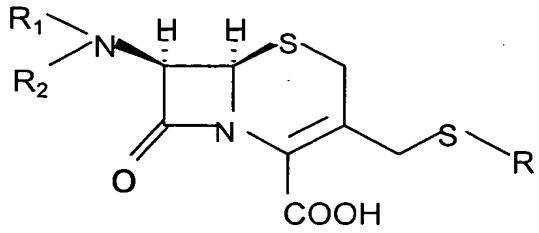
61. A process for preparing cephalosporanic acid dervatives comprising the step of:

enzymatically converting a compound of formula IV



(IV)

to form a compound of formula I



(I)

wherein R is a heterocyclic group comprising at least one nitrogen atom and R_1 and R_2 are both hydrogen atoms or one of them is a hydrogen atom and the other is an acyl donor.

62. A process as claimed in claim 61 wherein a compound of formula IV is enzymatically converted to form a compound of formula I with Glutaryl-7-ACA acylase.